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Application No. **10/677,956**	Filing Date **10/01/2003**	Examiner **Zachariah Lucas**	Customer No. **41576**	Group Art Unit **1648**

Invention: **METHOD AND SYSTEMS FOR PRODUCING RECOMBINANT VIRAL ANTIGENS**

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Response to Notification of Non-Compliant Appeal Brief

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:	Group Art Unit: 1648
ZEBEDEE et al.	Examining Attorney: Zachariah Lucas
Serial No.: 10/677,956	
Filed: October 1, 2003	Date: March 13, 2008 Pasadena, California
For: METHODS AND SYSTEMS FOR PRODUCING RECOMBINANT VIRAL ANTIGENS	

RESPONSE TO NOTIFICATION OF NON-COMPLIANT APPEAL BRIEF

In response to the Notification of Non-Compliant Appeal Brief dated March 4, 2008.

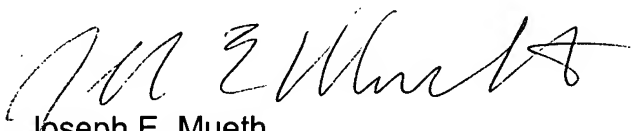
Regarding Section 3, the claims on appeal are 141, 143, 144, 146 and 147. Claims 140 and 142 are allowed. Claim 145 is withdrawn. All other claims have been cancelled.

The section 5 summary has been revised to reference each independent claim by page and line number to the Substitute Specification filed September 7, 2006.

Per our conversation today with Ms. Lorenda Hood, Patent Appeal Center Specialist, the corrected Appeal Brief is attached hereto in its entirety for The Board of Appeals and Interference's ease of reference.

Dated: March 13, 2008

Respectfully submitted,



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1. Real Party In Interest

The real parties in interest are the applicants' assignees, Bioprocess Pty Ltd and F. Hoffmann-La Roche Ltd.

2. Related Appeals and Interferences

There are no related appeals and interferences.

3. Status of Claims

Claims 140 to 144, 146 and 147 inclusive are pending. Claims 140 and 142 are allowed. Claims 141, 143, 144, 146 and 147 are being appealed. Claim 145 is withdrawn. All other claims have been cancelled.

Claims 141, 143, 144, 146 and 147 are finally rejected under 35 U.S.C. 103(a) as being unpatentable over Houghton et al., United States Patent No. 5,350,671.

4. Status Of Amendments

An amendment was filed on October 26, 2007 subsequent to final rejection. The Advisory Action of December 10, 2007, paragraph 7, indicates that the Amendment has been entered for purposes of appeal.

5. Summary Of Claimed Subject Matter

The invention relates to the detection of NANBV infection. This viral disease is otherwise known as "HCV" or "Hepatitis C". This invention as defined in independent claim 141 comprises the method for detecting seroconversion associated with NANBV infection at early times after infection by initiating an immunoreaction by contacting a body fluid sample with a NANBV capsid antigen and C-100-3 antigen; maintaining the immunoreaction for a time period sufficient to allow antibodies against the NANBV capsid and C-100-3 antigens present in said body fluid sample to immunoreact with the NANBV capsid and C-100-3 antigens to form immunoreaction products; and detecting the presence of any immunoreaction products formed and thereby detecting early seroconversion. The general methodology is disclosed, Specification, page 7, last four lines through page 8, last line, page 70, second full paragraph. The early detection of NANBV antibody with NANBV capsid antigen in an immunoassay together with detection of NANBV antibody with C-100-3 antigen is described in detail, Specification pages 100 to 106. The combination of capsid antigen with C-100-3 antigen is

disclosed, Specification, page 75, last paragraph.

Dependent claim 143 further specifies the detecting step (c) in claim 141 by admixing the immunoreaction products formed in step (b) with a labeled specific binding agent to form a labeling admixture, the labeled specific binding agent comprising a specific binding agent and a label; maintaining the labeling admixture for a period sufficient for any of the immunoreaction products present to bind with the labeled product; and detecting the presence of any labeled product formed, and thereby the presence of immunoreaction products. The labeled specific binding agent is disclosed, Specification page 21, second paragraph.

Claim 144 depends from claim 143 and specifies that the specific binding agent is Protein A, anti-human IgG or anti-human IgM. These binding agents are disclosed in the Specification page 67, second full paragraph.

Claim 146 depends from claim 143 and further specifies that the antigens are affixed to a solid matrix. The solid matrix is disclosed, Specification, page 68 last paragraph.

Claim 147 depends from claim 143 and further specifies that the antigens are comprised of a fusion protein. The fusion protein preparation is described in Examples 10 through 14, page 95, middle of the page at "EXAMPLE 10" through page 100, first

two lines.

6. Grounds Of Rejection To Be Reviewed On Appeal

The issues on appeal are as follows:

1. Claims 141, 143, 144, 146 and 147 are finally rejected under 35 U.S.C. 103(a) as being unpatentable over Houghton, et al., United States Patent No. 5,350,671 ('671).

The Appendix hereto contains a true copy of the claims on appeal.

7. Argument

1. The Rejection Of Claim 141, 143, 144, 146 and 147 On Houghton, et al. '671 Under 35 USC 103(a).

In the Brief, we first show that Houghton does not provide a basis for a finding that the claimed subject matter was prima facie obvious. Then we will show that all of the "secondary considerations" weigh in Appellant's favor.

By way of background, NANBV is a serious viral disease. The cDNA sequence of NANBV containing about 9300 nucleotides together with the encoded polyprotein encompassing a sequence of some 3000 amino acids were reported in the late 1980s. These sequences appear in Figures 89 and 90, respectively of the '671 patent.

In the following discussion, we refer to two NANBV peptide sequences, "capsid antigen" and "C-100-3" antigen. The capsid antigen, sometimes referred to as "core" antigen, refers to peptide sequences within and including up to about the first 122 amino acids of the NANBV polypeptide. The C-100-3 antigen refers to fusion protein which includes amino acids 1569 to 1931 (which sequence is usually referred to simply as "C-100") of the NANBV polypeptide.

An antibody, a protein generated by the immune system, is capable of recognizing and binding to a specific antigen. Described in terms of its structure, an antibody is a Y-shaped protein having primarily two regions: a variable region and a constant region. The variable region, located on the ends of the arms of the Y, binds to and interacts with the target antigen. This variable region includes a complementary determining region (CDR) that recognizes and binds to a specific binding site or epitope on a particular antigen. A target antigen generally has numerous binding epitopes, recognized by CDRs on multiple antibodies. Each antibody that specifically binds to a different epitope has a different structure.

In some diseases, the immune system produces multiple antibody types. One antibody type binds with at least one of the epitopes of a given antigen and another different antibody type does not bind with any epitope of the given antigen, but does bind with an epitope on a distinctly different antigen. Appellant has found that NANBV is such a disease.

Prior to the invention, it had been reported in the literature, that the state-of-the art antigen used for in-vitro testing for the presence of NANBV antibody (the C-100 antigen) did detect antibodies in infected persons, but did so primarily in individuals who found themselves in, or progressing towards, the chronic stage of the disease - in other words, a considerable time period had had to elapse following the infectious event before the presence of such anti-C-100 antibodies became detectable, instant Substitute Specification, filed September 7, 2006, at page 4, second paragraph.

In any disease, including the disease caused by the hepatitis C virus, early detection is of paramount importance not only because therapeutic intervention may have far better chances of success if initiated as early as possible in the disease, but also to prevent an inadvertent infection of others, for instance by eliminating hitherto undetected NANBV-infested blood donations from the inventory of transfusion services. Tainted blood supplies pose a significant public health risk. Therefore, there can be little doubt that detecting a seroconversion early in an individual who has become infected by the hepatitis C virus -as early as possible- is critically important. Having no antigen

at all available, or only one which is known to be deficient in its very capacity to do so, constituted a human health tragedy and a public health hazard.

The common failure to detect NANBV infection in cases of active infection, in individuals and blood banks, sometimes referred to as "false negatives", has been greatly reduced by the present invention.

Generic claim 141 is to the use of the combination of the capsid antigen and C-100-3 antigen. Appellant discovered that the capsid antigen detects the antibodies associated with early seroconversion. At a late or chronic stage following NANBV infection, the antibodies in a sample are primarily anti-C-100 antibodies and Appellant found that such samples do not necessarily react with the capsid antigen, see Substitute Specification, page 104, Table 5, chimp 10, week 51 where there was no reaction with the capsid antigen. These results as disclosed in the present patent application revealed for the first time the important benefit to be derived from using capsid antigen which Appellant found to bind to anti-capsid antibodies (not recognized by C-100 antigen), thus providing for detection of HCV seroconversion at early times after infection, and when used in conjunction with the C-100-3 antigen ("Anti HCV" in Table 5), detecting infection over the full span of times following exposure to NANBV.

Thus, Appellant discovered several closely linked phenomena: (1) NANBV infection results in the immune system producing more than one antibody type, (2) capsid antigen detects the antibody associated with early NANBV infection and (3) capsid antigen alone is not reliable for the detection of the different antibody type associated with chronic or late NANBV infection. It follows from the discovery of (1) to (3), that capsid and C-100 antigens used together reduce the incidence of false negatives below the level provided by the use of either capsid antigen or C-100 antigen alone.

The use of both the capsid antigen and the C-100-3 antigen in an immunoassay greatly minimizes the risk of false negatives because the individual patient does not present as "early" or "late" infected. Thus, each antigen contributes to an overall major benefit in the detection of a wide range of HCV infections, both early and late, when applied to the populace at large.

The Houghton '671 patent did not make obvious the combination of the capsid antigen with the C-100-3 antigen for any reason. The Examiner's focus on '671, Figure 65 and related discussion is unjustifiably narrow and is guided by improper hindsight as we will now demonstrate. Further, upon full comprehension of what the data of Figure 65 mean, it becomes clear that Houghton teaches away from the combination of capsid and C-100.

Preliminarily, it is important to recognize that the '671 patent disclosure is in many respects quite rudimentary. From subsequently gained knowledge, some of the results shown in '671 will be seen to be anomalous and an artifact of crude screening. Note that the two capsid antigens, CA 279a and CA290a are not the antigens actually brought to any particular degree of purity per the '671 patent. The cloning of clone CA290a is disclosed on column 64, lines 22 to 24. The clones themselves were not as such, engineered into expression vectors of the type disclosed for any of the other "very immunogenic" clones, but were seemingly only listed as clones by virtue of their identification upon screening of the lambda gt11 library. Column 82, line 40 to column 83, line 16, disclose how these clones were used; "Expression products of the indicated HCV cDNAs were tested for antigenicity...". Thus, the clones were identified as HCV positive by replica plating on to nitrocellulose followed by washing procedures and addition of various HCV serum specimens. This is the crudest form of assay and is an initial screening procedure at best. It is also impossible definitively to reproduce. The level of expression, and the antigenicity of the expressed polypeptides is not known, nor their three-dimensional configuration or the presence or absence of potentially present contaminants and interfering structures. It is thus reasonable to conclude that these antigens, obtained as disclosed in the '671 patent, did in fact fail to serve as a marker of early HCV infection. These facts show that clones expressed in gt11 libraries are unpredictable in their actual ability to form antigen-antibody complexes suitable to reliably and unequivocally demonstrate the true characteristics of such complexes. Consequently, based on the crude production method of the '671 patent, the CA279a

and CA290a clones may have been unsuitable for adequate presentation of crucial epitopes even if one were to look for early markers of disease. Therefore, that property may not have been an inherent property of the antigens obtained as disclosed in the '671 patent. This conclusion is supported by the data shown in Figure 65, which provides not the slightest indication of early detection being an inherent property of the capsid antigens as disclosed. (In fact, the opposite appears to be the case).

The single reference in Houghton to the immunologic reactivity of capsid antigens to NANBV antibodies reads as follows, '671, column 83, lines 16 to 53:

> As seen from the results shown in FIG. 65, a number of clones expressed polypeptides containing HCV epitopes which were immunologically reactive with serum from individuals with NANBH. Five of these polypeptides were very immunogenic in that antibodies to HCV epitopes in these polypeptides were detected in many different patient sera. The clones encoding these polypeptides, and the location of the polypeptide in the putative HCV polyprotein (wherein the amino acid numbers begin with the putative initiator codon) are the following: clone 5-1-1, amino acids 1694-1735; clone C-100, amino acids 1569-1931; clone 33c, amino acids 1192-1457; clone CA279a, amino acids 1-84; and clone CA290a amino acids 9-177. The location of the immunogenic polypeptides within the putative HCV polyprotein are shown immediately below.

Clones encoding polypeptides of proven reactivity with sera from NANBH patients:	
Clone	Location within the HCV polyprotein (amino acid no. beginning with putative initiator methionine)
CA279a	1–84
CA74a	437–582
13i	511–690
CA290a	9–177
33c	1192–1457
40b	1266–1428
5-1-1	1694–1735
81	1689–1805
33b	1916–2021
25c	1949–2124
14c	2054–2223
8f	2200–3325
33f	2287–2385
33g	2348–2464
39c	2371–2502
15e	2796–2886
C100	1569–1931

Figure 65 presents the antigenicity of polypeptides expressed from HCV cDNA clones used in an antigenic mapping study of the putative HCV polyprotein, '671, column 11, lines 1 et. seq. Of the polypeptides of Figure 65, the seventeen (17) listed above were identified in the '671 patent as immunologically reactive with sera from individuals already known to be NANBV positive. Upon inspection of Figure 65, it appears that samples 1 to 4 in this series were not tested at all with the capsid antigens identified in Figure 65 as CA 259a and CA 290. In fact, or at least apparently, only four samples actually were tested. There is no useful legend to Figure 65, but Figure 65 indicates the outcome of an individual test result with either a plus (+) sign or a minus (-) sign. The samples 1 to 4 of "Chronic HCV Patient C-100 positive" has neither entry for the two capsids, it is blank. Therefore, samples 1 to 4 appear not to have been tested at all with the capsid.

Figure 65 of the '671 patent does not provide any evidence that the capsid antigen, as presented in its specification, did detect seroconversion at early times after infection. In fact, the data presented teach away from such an interpretation. Specifically, in Figure 65, Houghton appears to score, as capsid reactive samples, the last four specimens in a collection of sera labeled as "Chronic HCV patient C-100 positive" (all eight of these specimens scored as positive when tested with C-100). First, these specimens are stated to have originated from a chronic patient, i.e., someone who has passed the acute state, thus seemingly recovered from the acute sequelae but who still exhibits some evidence of continued disease, i.e., entered a chronic state of the disease process. While not unequivocally clear, the most reasonable reading is that these eight specimens were obtained in some temporal sequence, specimen no. 1 obtained some time before specimen no. 2, and so on, albeit no definitive information is given in the '671 disclosure hereto. On this basis, it is noteworthy that, if anything, a person interested to investigate whether a certain antibody specificity – say, to the capsid -- might appear, (or disappear), in the course of the disease, would have tested all eight specimens in order to delineate the characteristics of said test antigen. Evidently, all eight specimens did show reactivity with the C-100 antigen, but we do not know if this is also a correct result for the capsid antigen(s), since only the last four specimens (no. 5-8) were – apparently -- investigated in this regard. For this series of specimens to have any conceivable, predictable power with regard to the properties of the capsid antigen, one would have to have been interested to determine the reactivity profile of all eight specimens. Based on the data

presented regarding these specimens, therefore, it is concluded that Houghton provides no motivation, or even the remotest suggestion that the capsid had, in fact, exhibited a unique capacity to serve as an early marker for the appearance of anti-HCV antibodies.

This lack of motivation is further supported and enhanced by the outcome when considering , in Figure 65 of the '671 patent, two additional specimens, labeled as "1. Post acute" and "2. Post acute". It is likely, since these were sera taken from chimpanzees, that they may have been obtained in a documented fashion and that they may indeed have been specimens even taken early after a deliberate infection had been induced. Each of these specimens were apparently tested with both capsid related antigens as well as with the C-100 antigen. Assuming that the test performed, using the two capsid related antigens as disclosed by Houghton, actually should have reflected their capability for detecting antibody at early times after infection, they fail in this test, because they both scored as nonreactive with either capsid antigen. The C-100 antigen also scored as negative with these two sera. Thus, in both cases, the test result was negative thus solidifying Houghton's (incorrect) conclusion, that the capsid and C-100 antigens were actually, similar in their reactivity patterns ("all very immunogenic"). At the same time, the test result evidences that Houghton never had pure capsid antigen and strongly suggests that his purported capsid antigens were impure. Thus, these results fail to provide an indication of the capacity of the capsid to react differently than C-100. To the contrary, the results reported in Figure 65 would suggest that the capsid and C-100 in combination would perform much as either

antigen singly. Therefore, Houghton does not provide a reason to combine capsid with C-100, and instead, teaches away from the combination of capsid and C-100.

A final sample, identified as "Convalescent, C-100 negative" scored as reactive with the capsid. Other than being identified as "C-100 negative" the etiology of such specimen is completely unclear. Convalescent? Since when? A literal definition of convalescence as provided by Wikipedia is (note: an irrelevant sentence in the definition given verbatim below, for the purpose of this action, has been bracketed) as follows:

> Convalescence is the gradual recovery of health and strength after illness. [The convalescence of a patient after a life altering surgery or illness is greatly affected by the volunteers and health care providers.] It refers to the later stage of an infectious disease when the patient recovers and returns to normal, but may continue to be a source of infection even if feeling better.

"Convalescent C-100 negative" is thus a vague term which might be taken to imply a point in time when someone is at some stage of recovery from disease, but there is no suggestion in '671 that this serum originated from a specimen taken at early times after infection – indeed, "convalescent" refers to a later stage of an infectious disease.

In summary, therefore, neither Houghton, nor anybody else, was in a position to conclude from these '671 data what the Appellant discovered, and provided unequivocal evidence for, namely, that the capsid is able to detect HCV antibody at early times after infection, and furthermore, that the capsid might fail in detecting HCV antibody in situations where the C-100 antigen still did, and, hence, that combining the two antigens was indeed unobvious. More fundamentally, given the data and disclosure of the '671 patent and the subsequent realization that C-100 alone failed to detect certain HCV antibody, one skilled in the art probably would have looked for a substitute for C-100 and that substitute would not have been the capsid since Houghton reported these two antigens to be basically the same in their reactivity with HCV antibody. There was nothing in the '671 that would have caused one skilled in the art to choose the capsid for combination with C-100.

The term "very immunogenic" as used in the '671 patent is meaningless in the context of the detection of early seroconversion since Houghton's serum samples were from patients already known to be seropositive and his grading of the reactivity of the seventeen (17) antigens with these serum samples could not reveal anything about when seroconversion took place. In the'671 patent, there is no discrimination between the five antigens provided as they are merely stated to be "very immunogenic", all similar. It was the Appellant here who discovered they are not similar and that capsid and C-100 antigens react with different antibodies. More significantly, since the '671 patent never discloses which antibodies were detected by any of the seventeen (17)

antigens, the patent teaches nothing about the detection of early seroconversion, that is, no teaching that any of the myriad possible combinations of the antigens would detect early seroconversion and, of course, no motivation to combine capsid antigen with C-100 antigen or expectation of success.

While Houghton presents seventeen antigens of which five are "very immunogenic" antigens which he disclosed can be used in panels, he does not show any combinations and numerous combinations of the seventeen are possible (pairs, triplets, etc.). Therefore it is unreasonable to conclude that all of the hundreds and thousands of combinations were obvious given the large number of possible combinations, especially since Houghton provides no reason to expect that any combination will reduce the incidence of false negatives.

Solving the problem of false negatives resulting from the use of C-100-3 alone in an immunoassay, in the first instance, would not have motivated those skilled in the art to try other antigens or antigen combinations in an immunoassy, a Herculean task in itself, since a priori, one skilled in the art would not have reason to attribute the non-detection problem to the antigen. At the time, NANBV immunoassays were of recent vintage. Immunoassays may fail due to many causes unrelated to the antigen. For example, the problem might have been caused by unknown but interfering natural components in the patient samples or to some problem or lack of refinement of assay procedure or technique. The fact that it was known that C-100-3 antigen based assays

were deficient did not mean that C-100-3 antigen was at the source of the deficiency anymore than it meant that substituting some other antigen or combining antigens would overcome the deficiency.

Further, even when focusing on the antigen used, there was nothing in the '671 patent that would motivate one to use the specific combination of capsid antigen and C-100-3 antigen in an immunoassay. The seventeen listed antigens included C-100, and two antigens from the capsid, viz., CA 279 and CA 290. However, given the failure of C-100 to detect early infection, and the report in the '671 patent that C-100, CA 279 and CA 290 were all "very immunogenic" without recognition of any relevant difference in the immunogenic properties of these antigens compels the conclusion here that this disclosure of the '671 patent did not establish any reasonable expectation that any combination of the very immunogenic antigens or any of the other of the seventeen listed antigens including CA 279 and CA 290 would serve any purpose, or perform any better than C-100 alone, much less provide detection of early infection.

Moreover, to focus on C-100, CA 279 and CA 290 is simply impermissibly narrow. The Examiner is engaged in hindsight. The NANBV polypeptide contains about 3000 amino acid residues and nothing in the '671 patent provides a reason to select any particular peptide sequence with the expectation that it would detect NANBV infection at early times. Even after eliminating as the source of the non-detection of early infection causes extraneous to the structure of the antigen, one skilled in the art

was left with millions of peptide sequence pairs and other combinations thereof, etc., all from the NANBV polypeptide as possibly having the requisite reactivity required for detection of early NANBV infection. Finally, even after Appellant discovered the critically important and unique ability of the capsid to detect early infection, Appellant also discovered that such was not enough inasmuch as it is necessary to join the capsid with C-100-3 to provide the maximum temporal detection span.

The Examiner argues that the '671 patent teaches the use of both the C-100-3 antigen and the core antigen for the detection of anti-HCV antibodies and therefore it would have been obvious to those of ordinary skill in the art to combine these antigens, because it was known in the art that the C-100-3 antigen alone did not detect all cases of HCV infection contrary to Figure 65. This is just a claim that those of ordinary skill in the art would have had motivation to combine the use of the capsid antigens listed in the '671 patent with the use of the known C-100-3 antigen which cannot be sustained for the reasons stated above based on the teachings of the '671 patent.

The results shown in the '671 patent taken with the subsequent finding that the antibodies associated with early infection were not detected by C-100 meant that none of the '671 antigens actually shown to have been tested in the '671 patent were likely candidates antigens for the detection of early antibodies. The '671 patent did not provide a group of candidate antigens from which those skilled in the art might be expected to select and combine. Instead, it presented a logical dead end. The '671

patent simply did not provide a logical point of departure leading to an immunoassay for the detection of both early and late antibodies.

The '671 patent does not provide any reason or motivation to combine the specific antigens claimed here. The Examiner seems to suggest that because C-100-3 alone was inadequate for early detection this very inadequacy provided motivation to combine it with other antigens, and specifically with the capsid antigen which, however, had not been known to detect early infection either, or that one antigen was better than another. There is no evidence establishing prima facie obviousness because the '671 patent never recognized that the disclosed antigens react differently, the capsid preferentially with antibodies present at the early infection stage and C-100 with antibodies present at the post acute or chronic stage.

The Examiner's argument amounts to an assertion that the use of the two specific antigens in the claimed combination was obvious when in fact, the possibilities facing those skilled in the art faced with the problem of false negatives were varied and numerous.

The Examiner acknowledges that the Houghton '671 patent does not disclose the combination of the capsid and C-100-3 antigens in an immunoassay for NANBV infection. The '671 patent never recognized that different NANBV infection stages present different antibodies requiring different antigens for their detection. Thus, it

follows that the subject matter of claim 141 is not "inherent" in Houghton. Houghton does not disclose the use of the combination of the two specific antigens. "Obviousness cannot be predicated on what is not known at the time the invention is made, even if the inherency of a certain feature is later established, In re Riukaert, 9 F3d 1531, 28 USPQ 2d 1955 (CAFC 1993)", per MPEP 2141.02, p. 2100-125. Riukaert is dispositive of the inherency issue in this case, see Riukaert at p. 1957, 28 USPQ 2d:

> 'The mere fact that a certain thing *may* result from a given set of circumstances is not sufficient [to establish inherency.]' In re Oelrich, 666 F.2d 578# 581-82, 212 USPQ 323, 326 (CCPA 1981) (citations omitted) (emphasis added). 'That which may be inherent is not necessarily known. Obviousness cannot be predicated on what is unknown.' In re Spormann, 363 F.2d 444, 448, 150 USPQ 449, 452 (CCPA 1996). Such a retrospective view of inherency is not a substitute for some teaching or suggestions supporting an obviousness rejection. See In re Newell, 891 F.2d 899, 901, 13 USPQ2d 1248, 1250 (Fed. Cir. 1989).

The Supreme Court's latest word on obviousness and combination inventions is found in KSR International Co. v. Teleflex, Inc., 127 S.Ct. 1727, 82 USPQ 2d 1385 (2007). KSR clearly requires a common sense approach to assessing the obviousness of "combination" inventions. In KSR , the Court did not totally reject the Federal

Circuit's teaching, suggestion or motivation (TSM) test - only a "rigid" approach to that test. It acknowledged that most inventions are combinations of prior art elements. It indicated that the "teaching, suggestion or motivation" test had "no doubt" been applied in accordance with Supreme Court precedent "in many cases."

The recently decided, post-KSR case, Takeda Chemical Industries Ltd. v. Alphapharm Pty. Ltd., 492 F.2d 1350, 83 USPQ 2d 1169 (Fed. Cir. 2007), is instructive. The case involved a specific TZD compound, the active ingredient in a drug widely used for type 2 diabetes, known as ACTOS and, chemically, as pioglitazone. The prior art '200 patent disclosed a vast array of TZD compounds including compound "b", the adjacent homolog of ACTOS. Other prior art (Sodha II) disclosed 101 TZD compounds having hypoglycemic activity including compound b (and also disclosing that compound "b" had undesirable side effects), and another prior art patent, ('779), characterized compound "b" as "especially important". The Federal Circuit sustained validity of the ACTOS composition-of-matter claims over the prior art:

> The KSR Court recognized that "[w]hen there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp." KSR, 127 S.Ct. at 1732. In such circumstances, "the fact that a combination was obvious to try might show that it was obvious under § 103." Id. That is not the case

here. Rather than identify predictable solutions for antidiabetic treatment, the prior art disclosed a broad selection of compounds any one of which could have been selected as a lead compound for further investigation. Significantly, the closest prior art compound (compound b, the 6-methyl) exhibited negative properties that would have directed one of ordinary skill in the art away from that compound. Thus, this case fails to present the type of situation contemplated by the Court when it stated that an invention may be deemed obvious if it was "obvious to try." The evidence showed that it was not obvious to try.

The instant case bears close parallel to Takeda Chemical in that the '671 patent disclosed a broad selection of antigens any one or ones of which could have been selected as the lead antigen for further investigation, but the most highly immunogenic of which were reported to be the same as C-100, a failure in the detection of early NANBV detection. Thus, as in Takeda Chemical, this is not a case where it was obvious to try. Rather, the prior art shows that it was not obvious to try.

The Examiner argues that while the problem of early detection is not recognized in the '671 patent, the basis for finding an invention obvious need not rely on the same motivation or rational for the modification of the prior art as the Applicant, citing MPEP § 2144. (The latest version, published September 2007, does not address KSR or Takeda Chemical.) The test for prima facie obviousness for immunoassays is

consistent with the legal principles enunciated in KSR. While the KSR Court rejected a rigid application of the teaching, suggestion, or motivation ("TSM") test in an obviousness inquiry, the Court acknowledged the importance of identifying "a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does" in an obviousness determination. KSR, S.Ct. at 1731. Also, Takeda Chemical, supra. Thus, in cases involving new immunoassays, it remains necessary to identify some reason that would have led an immunologist to modify a known assay in a particular manner to establish prima facie obviousness of a new assay.

In KSR, the Court acknowledged that a requirement that a "teaching, suggestion, or motivation to combine known elements" be demonstrated to show that a combination of prior art elements is obvious "captured an helpful insight." Common sense dictates that a patent claim to "a combination of two known devices" be looked at with care, but it "can be important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements" as in the claim. Most inventions are combinations of what is known.

The Federal Circuit has linked to its TSM test a further requirement: there must have been "a reasonable expectation of success" in making an invention consisting of a combination of prior art elements. This might be called the TSM+ (plus) test.

In KSR, the Supreme Court did not disturb the expectation of success concept, and in fact, appears to have agreed with it. At one point, the patent owner in KSR argued that the prior art elements "cannot be combined" as in the patent claim in question. The Supreme Court held that this argument had not been raised in the lower courts "in a clear fashion," but it appeared to assume that evidence of difficulties or unpredictability in combining prior art teachings might render a combination non-obvious. The present claim 141 is allowable under the TSM+ test since the '671 patent merely discloses an array of polypeptides from HCV and never recognized the difficulty of isolating the specific ones which would provide detection of HCV seroconversion at both early and chronic infection stages. Houghton does not disclose any guidance in this area and hence applicants' discovery of a method which does detect seroconversion at both stages and reduce false negatives was completely unpredictable.

The Examiner further argues that if there is any unexpected result to be seen, it is not from the combination of the two antigens, but it is from the use of the capsid antigens themselves, Advisory Office Action of December 10, 2007. The Examiner is wrong about this and wrong when he states that those of ordinary skill in the art would have been motivated to use the combination of the two antigens for the detection of HCV antibodies, "as the benefits of the claimed invention would naturally flow from the combination of the capsid protein with any HCV antigen". This is wrong because it was not taught in the '671 patent that the capsid antigen was distinguished by its ability to

detect early NANBV infection, but not always chronic or late NANBV infection, an insight leading to the combination with the C-100 antigen.

The '671 patent also fails to distinctly identify and point out the problem associated with serology based on the C-100-3 antigen in that the later antigen is not associated with detection of antibodies to HCV at early times after infection. The lack of acknowledgment of the problem inevitably leads to a failure to provide the solution to this problem, namely the provision of a method for detection at early times after infection (which method incorporates providing the capsid antigen encoded by HCV recited in claim 141). In fact, Houghton teaches away from the solution by merely disclosing that several of the seventeen (17) antigens were "very immunogenic", with patient samples - none of which reveal anything about reactivity with patient samples from early or acute infected patients, thus failing to discriminate between or recognize their distinct properties.

The Examiner acknowledges that Houghton does not teach the combined use of capsid with C-100-3 antigen. Further, as discussed above, Houghton did not disclose whether he had any early sera which were tested with capsid and did not teach that the capsid was uniquely effective in detecting early seroconversion and did not teach any way of minimizing the failure to detect early HCV infection. If the problem presented were early detection, one skilled in the art would not expect any of the other sixteen antigens to be better than C-100-3 in detecting early seroconversion, nor would one

expect any combination of the seventeen to detect early seroconversion.

In summary, Houghton fails to establish a prima facie case of obviousness of the subject matter of the instant claims.

The Court in KSR indicated that there is "no necessary inconsistency between the idea underlying the TSM test and the Graham analysis." Id. As long as the test is not applied as a "rigid and mandatory" formula, that test can provide "helpful insight" to an obviousness inquiry. Id.

Under Graham v. John Deere, 383 US 1, 148 USPQ 459 (1966), United States v. Adams, 383 US 39, 148 USPQ 479 (1966) and Federal Circuit law, so-called "secondary considerations" or "objective evidence", such as a patented invention's commercial success, long felt but unresolved need, failure of others, etc., frequently play a role in obviousness determinations. These considerations were considered by the Supreme Court in KSR to have continuing relevance. It noted that Graham "invited courts, where appropriate, to look at any secondary considerations that would prove instructive."

The Petition to Make Special, filed February 24, 2006, evidences the commercial importance of this invention.

As the Examiner notes, prior to the present invention it was known that C-100-3 did not detect all cases of seroconversion caused by HCV, Weiner et al, Lancet, 355:1-3 (1990), of record in the Information Disclosure Statement filed March 9, 2006. The known inadequacy of C-100-3 in the detection of some cases of seroconversion and the resulting incidence of false negatives is telling evidence of a felt need.

The failure of others including Houghton to satisfy that need are significant evidence of non-obviousness, Graham v. John Deere, supra.

Appellant solved a major public health problem.

All of these secondary considerations weigh in Appellant's favor.

The rejections on Houghton '671 should be reversed.

CONCLUSION

The Final Rejection should be reversed.

8. Claims Appendix

The appealed claims are set forth in the attached Claims Appendix.

9. Evidence Appendix

There is no evidence presented herein under 37 CFR §§ 1.130, 1.131 or 1.132.

10. Related Proceedings Appendix

No decisions related to the instant application have been rendered in a proceeding by a court or the Board.

Dated: March 13, 2008

Respectfully submitted,

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CLAIMS APPENDIX

PENDING CLAIMS IN U.S. PATENT APPLICATION

SERIAL NO. 10/677,956

Claim 140: A method for detecting seroconversion associated with NANBV infection at early times after infection comprising:

(a) initiating an immunoreaction by contacting a body fluid sample with NANBV capsid antigen having the amino acid sequence from residue 1 to 120 of SEQ ID NO: 73;

(b) maintaining said immunoreaction for a time period sufficient for allowing antibodies against the NANBV capsid antigen present in the body fluid sample to immunoreact with said NANBV capsid antigen to form an immunoreaction product; and

(c) detecting the presence of any of said immunoreaction product formed and thereby detecting early seroconversion.

Claim 141: A method for detecting seroconversion associated with NANBV infection at early times after infection comprising:

(a) initiating an immunoreaction by contacting a body fluid sample with a NANBV capsid antigen and C-100-3 antigen;

(b) maintaining said immunoreaction for a time period sufficient for allowing antibodies against the NANBV capsid and C-100-3 antigens present in said body fluid sample to immunoreact with said NANBV capsid and C-100-3 antigens to form immunoreaction products; and

(c) detecting the presence of any of said immunoreaction products formed and thereby detecting early seroconversion.

Claim 142: A method for detecting seroconversion associated with NANBV infection at early times after infection comprising:

(a) initiating an immunoreaction by contacting a body fluid sample with NANBV capsid antigen having the amino acid sequence from residue 1 to 120 of SEQ ID NO: 73 and C-100-3 antigen;

(b) maintaining said immunoreaction for a time period sufficient for allowing antibodies against said NANBV capsid and C-100-3 antigens present in the body fluid sample to immunoreact with said NANBV capsid and C-100-3 antigens to form immunoreaction products; and

(c) detecting the presence of any of said immunoreaction products formed and thereby detecting early seroconversion.

Claim 143: The method of claims 141 or 142 wherein said detecting in step (c) comprises the steps of:

(a) admixing said immunoreaction products formed in step (b) with a labeled specific binding agent to form a labeling admixture, said labeled specific binding agent comprising a specific binding agent and a label;

(b) maintaining said labeling admixture for a period sufficient for any of said immunoreaction products present to bind with said labeled product; and

(c) detecting the presence of any said labeled product formed, and thereby the presence of said immunoreaction products.

Claim 144: The method of claim 143 wherein said specific binding agent is selected from the group consisting of Protein A, anti-human IgG and anti-human IgM.

Claim 145: The method of claim 143, wherein said label is selected from the group consisting of lanthanide chelate, biotin, enzyme and radioactive isotope.

Claim 146: The method of claim 143, wherein said antigens are affixed to a solid matrix.

Claim 147: The method of claim 143, wherein said antigens are comprised of a fusion protein.

EVIDENCE APPENDIX

EVIDENCE PRESENTED IN U.S. PATENT APPLICATION

SERIAL NO. 10/677,956

There is no evidence presented herein under 37 CFR §§ 1.130, 1.131 or 1.132.

RELATED PROCEEDINGS APPENDIX

DECISIONS AND PROCEEDINGS RELATED TO U.S. PATENT APPLICATION

SERIAL NO. 10/677,956

There are no related decisions or proceedings pending in this country.